Re-infection with SARS-CoV-2 in Patients Undergoing Serial Laboratory Testing

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Summary: Re-infection **with SARS-CoV-2** was **infrequent, occurring in 63 (0.7%) of 9,119 patients, but was associated with two deaths**. Re-infection appeared to be milder than primary infection.

ABSTRACT

Background: A better understanding of re-infection after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has become one of the healthcare priorities in the current pandemic. We determined the rate of re-infection, associated factors and mortality during follow up in a cohort of patients with SARS-CoV-2 infection.

Methods: We analyzed 9,119 patients with SARS-CoV-2 infection who received serial tests in total of 62 healthcare facilities **in United States between December 1, 2019 to November 13, 2020**. Re-infection was defined by two positive tests separated by interval of greater than 90 days two after resolution of first infection was confirmed by two or more consecutive negative tests. We performed logistic regression analysis to identify demographic and clinical characteristics associated with re-infection.

Results: Re-infection was identified in 0.7% (n=63, 95% confidence interval [CI] 0.5%-0.9%) during follow up of 9,119 patients with SARS-CoV-2 infection. The mean period (±standard deviation [SD]) between two positive tests was 116 ± 21 days. A logistic regression analysis identified that asthma (odds ratio [OR] 1.9, 95% CI 1.1-3.2) and nicotine dependence/tobacco use (OR 2.7, 95% CI 1.6-4.5) were associated with re-infection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with re-infection compared with primary infection among the 63 patients with re-infection There were two deaths (3.2%) associated with re-infection.

Conclusions: We identified a low rate of re-infection confirmed by laboratory tests in a large cohort of

patients with SARS-CoV-2 infection. Although re-infection appeared to be milder than primary infection,

there was associated mortality.

Key words: Reinfection; Coronavirus; SARS-CoV-2; COVID-19; Laboratory tests.

By October 2020, five cases of re-infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) had been reported from Hong Kong, Belgium, the Netherlands, Ecuador, and United States[1-5] when over 37 million SARS-CoV-2 infected persons had been reported worldwide.[6] A better understanding of re-infection became one of the priorities for Centers for Disease Control and Prevention to inform public health action.[7] Identification of characteristics and frequency of reinfection was considered crucial by the European Centre for Disease Prevention and Control[8] due to implications for duration of acquired immunity, The results of SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN)[9] were made available in January 2021. Between 18 June and 09 November 2020, 44 re-infections (2 probable, 42 possible) were detected in the baseline positive cohort of 6,614 healthcare workers. The study investigators acknowledged that there is paucity of data regarding re-infection limiting our understanding of public health implications. A better understanding of the risk of re-infection is necessary from the public health perspective and may have implications for vaccination strategy.

METHODS

Patients

We analyzed data from the Cerner de-identified Coronavirus Disease 2019 (COVID-19) dataset. This is a subset of Cerner Real-World Data extracted from the electronic medical records of health care facilities which have a data use agreement with Cerner Corporation.[10, 11] Patients with a positive laboratory test for SARS-CoV-2 were identified based on Logical Observation Identifiers Names and *Codes* (*LOINC®*) 41458-1, 94309-2, 94500-6, 94533-7, 94534-5, and 94646-7. These codes denote

detection of SAR-CoV-2 ribonucleic acid in respiratory (nasopharyngeal swabs, bronchoalveolar lavage, sputum) and other specimens or detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions, all by nucleic acid amplification with probe detection. The Food and Drug Administration has only approved assays for detection of SARS-CoV-2 N gene or RdRp gene in respiratory secretions in United States.

The methodological aspects of the dataset are available in other publications.[12, 13] The Cerner Real-World Data-COVID-2020 Q3 version of the data included data from 62 contributing Cerner Real-World Data health systems in United States. The data is based on electronic medical records between December 1, 2019 to November 13, 2020. The dataset, as part of the de-identification procedure, does not provide an identifier for the medical institution of a patient's data or its precise location. Our analysis included patients with at least one COVID-19 related inpatient or emergency department (ED) encounter who tested positive for COVID-19, had at least one medical encounter on record prior to their first COVID-19 related encounter, and who received at least four reliable COVID-19 tests which were conclusive.

Re-infection was defined by two positive tests separated by interval of greater than 90 days two after resolution of first infection was confirmed by two or more consecutive negative tests consistent with definitions used in previous reports.[9, 14, 15] The associated medical diagnoses and outcomes were identified using *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes in the medical records at time of primary infection, and the re-infection. *ICD-10-CM* codes were used to identify the patients with hypertension (I10, O10.0, O10.9, I16 and I67.4), diabetes mellitus

(E08, E09, E10, E11 and E13), atrial fibrillation (I48), hyperlipidemia (E78), stroke (I60, I61, I62.9, I63, I65, I66), heart failure (I50), malignancy (Z85, C80.1), chronic obstructive pulmonary disease (COPD) (J44), asthma (J45), chronic kidney disease (CKD)/end-stage renal disease (ESRD) (N18), nicotine dependence/tobacco use (F17, Z72.0), pneumonia (J12-J18), urinary tract infection (N30.9), acute kidney injury (N17), septic shock (R65.21), hepatic failure (K72, K74.3-K74.6), respiratory failure (J96), cardiac arrest (I46), thrombosis/pulmonary embolism (I26, I74, I75, I82.40-I82.44, I82.49, I82.4Y, I82.4Z), encephalopathy (G93.4), ST-elevated myocardial infarction (STEMI) (I21.0-I21.3), non-ST elevated myocardial infarction (NSTEMI) (I21.4). Intubation and mechanical ventilation were identified by ICD-10-CM codes 0BJ17EZ and Z9911 or current procedural terminology codes 31500, 94656, and 94657 (for intubation) or 94002 to 94005 (for mechanical ventilation).

Discharge destination was categorized as home or non-routine discharge (acute rehabilitation, intermediate care, skilled nursing facility, or nursing home) during a SARS-CoV-2 infection related encounter.

Statistical analysis

A large proportion of patients in the dataset were excluded from the analysis due to lack of serial tests performed for detection of SARS-CoV-2. To better understand the selection bias, we compared patients' age, sex, race/ethnicity, cardiovascular risk factors, and medical complications between included and excluded patients.

We provided the rate of re-infection with 95% confidence interval (CI) without continuity correction.[16]

We compared patients' age, sex, race/ethnicity, cardiovascular risk factors, medical complications, and

discharge status (categorized into non-routine discharge, or expired in medical facility) for patients in

strata based on presence or absence of re-infection during follow up among patients with SARS-CoV-2

infection. We used the χ^2 test for categorical data and analysis of variance (ANOVA) test for continuous

variables. We performed logistic regression analysis including all patients with SARS-CoV-2 infection to

identify the associations between various demographic and clinical characteristics and odds of re-

infection. Stepwise feature selection was used to select variables. All the hypothesis tests were 2 sided,

with P<0.05 considered statistically significant, and all the analyses were done using R (version 3.6.1).

We also provided estimates for rates of re-infection defined using different cut-off periods for time

interval between first and second positive tests (>45 days, >60 days, >75 days, >90 days, and >105 days).

RESULTS

A total of 9,119 patients with SARS-CoV-2 infection met our inclusion criteria among 110,754 patients

with positive SARS-CoV-2 tests in the data. Compared with patients who were excluded, patients who

were included in the analysis were more likely to aged>65 years, African-American or Hispanic, and have

higher proportion of those with hypertension, diabetes mellitus, atrial fibrillation, nicotine dependence,

hyperlipidemia, prior stroke, COPD, asthma, and chronic kidney disease. Included patients also had a

higher proportion of patients with new stroke, heart failure, cardiac arrest, pneumonia, respiratory failure,

and acute kidney injury. The proportion of patients who required intubation/mechanical ventilation was higher in included patients.

Re-infection was identified in 0.7% (n=63, 95% CI 0.5%-0.9%) of the patients (see Table 1). The mean period (± standard deviation [SD]) between two positive tests was 116 ± 21 days. There were no significant differences based on age or sex among patients with and without re-infection. The proportion of patients categorized under other race/ethnicity was higher in those with re-infection. The proportion of patients with nicotine dependence/tobacco use, asthma, and COPD were higher in patients with re-infection. The proportion of patients with non-routine discharge were similar between re-infection and without re-infection groups. In the logistic regression analysis, patients with asthma (odds ratio [OR] 1.9, 95% CI 1.1-3.2), and nicotine dependence/tobacco use (OR 2.7, 95% CI 1.6-4.5) were at higher risk for re-infection. Furthermore, compared with White patients, the patients categorized as other race/ethnicity (OR 2.3, 95% CI 1.2-4.5) were associated with higher risk for re-infection.

There were two deaths (3%) associated with re-infection. There was a significantly lower rate of pneumonia, heart failure, and acute kidney injury observed with re-infection compared with primary infection among the 63 patients with re-infection (see Table 2). There was a trend towards lower rates of respiratory failure and hepatic failure during re-infection. Intubation/mechanical ventilation in two (3%) patients required during primary infection but in none of the patients during re-infection.

The rates of re-infection ranged from 0.4% to 2.2% using different cut-offs for time intervals between first and second positive tests for definition with decrease in rates observed with increase in time intervals (see Figure 1).

DISCUSSION

We found a low rate of re-infection (0.7%) with SARS-CoV-2 confirmed by laboratory tests based on the analysis of large cohort of patients in the Cerner Real-World data. The rate of re-infection was similar to the 0.66% rate reported in previous SIREN[9] study. SIREN study defined possible re-infection with two reverse transcription polymerase chain reaction (RT-PCR) positive samples 90 or more days apart (based on national surveillance analysis)[17] or an antibody positive participant with a new positive RT-PCR at least four weeks after the first antibody positive result. The rate of re-infection was 0.65% (95% CI 0.51–0.82) in an individual-level data analysis from the Danish Microbiology Database[15] The study used two positive RT-PCR tests, one performed before June 1, 2020 and second performed from Sept 1 to Dec 31, 2020 (minimum of 90 day interval) as evidence of re-infection. Other authors[14] have also recommended a time interval of 90 days to differentiate re-infection from relapse or re-positivity. The European Centre for Disease Prevention and Control[8] recognizes that longer time-interval between two RT-PCR positive samples increases the likelihood of re-infection as it relates to waning immunity and lower antibody levels. Re-detection of the primary episode is more likely the cause than a true re-infection with shorter period of time interval between two RT-PCR positive sample. We acknowledge that re-infection is possible within a time interval <90 days and therefore have also presented the rates

based on various time intervals used to define re-infection. The rates of re-infection ranged from 0.4% to 2.2% in our analysis using different cut-offs for time intervals between first and second positive tests (see Figure 1). Another analysis of national surveillance database in Qatar reported a re-infection rate of 0.01% (95% CI: 0.01-0.02%)[18] when re-infection was defined by ≥45 days interval between two RT-PCR positive tests. The longitudinal study of healthcare workers in Oxford University Hospitals[19] reported a rate of 0.2% when using a time interval of ≥60 days between detection of serum antibodies against SARS-CoV-2 and subsequent positive RT-PCR test to define re-infection and exclude patients with persistent viral shedding from initial infection. One of the 3 patients with re-infection had two positive RT-PCR tests separated by an interval of 190 days (5 negative tests in the interim period).

In our analysis, age of the patient at the time of initial infection was not associated with re-infection either in the univariate or stepwise logistic regression analysis. We compared occurrence of medical events reflective of multi-organ involvement or requirement of mechanical ventilation during initial SARS-CoV-2 infection between patients with or without re-infection (see Table 1) but did not identify any differences in surrogate markers of severity of infection between the two groups. Re-infection was associated with pre-existing asthma and nicotine dependence/tobacco use. Patients with asthma are at higher risk for respiratory viral infections[20] and an increased risk of H1N1 infection has been reported in children with asthma.[21] Cigarette smokers are also at high risk for viral infection including SARS-CoV-2.because of deficits in muco-ciliary clearance mechanisms and cell-mediated immunity in the lung alveolus. [22] Additional evidence of immunosuppression such as depressed migration and chemotaxis of leukocytes, reduced natural killer cell activity, and lower levels of circulating serum immunoglobulin levels have

been reported in cigarette smokers.[22] Cessation of cigarette smoking can result in recovery of immune function within 6-12 weeks.[23, 24].

In our analysis, re-infection appeared to have less severe manifestations than the primary infection with lower rates of pneumonia, heart failure, and acute kidney injury. However, there were two deaths (3.2%) associated with re-infection. There seems to be some controversy whether re-infection is a less severe or more severe disease compared with the primary infection.[25-28] Selvaraj et al. [29] reviewed 34 patients reported in the literature with re-infection and found variable severity of clinical manifestations. Patients with re-infection have antibodies against SARS-CoV-2 identified in serum at time of re-infection. [25-28] Therefore, persistent immunity may result in less severe manifestations of infection. However, antibody-dependent enhancement may facilitate viral entry during re-infection or exaggerated immune response may result in more severe manifestations.[30] We have to consider that survival in patients with SARS-CoV-2 infection has been improving over time[31] and appearance of less severe manifestations during re-infection may be partly due to more effective medical management in subsequent months. There is also another bias with patients with mild manifestations during initial SARS-CoV-2 infection being more likely to be more exposed to re-infection due to higher survival and shorter time in isolation.

Re-infection was initially attributed to heterogeneity in response and decline in immunity over time among patients with SARS-CoV-2 infection. Long et al.[32] and Muecksch et al.[33]reported a decline in IgG antibodies and neutralizing antibody against SARS-CoV-2 spike (S) or nucleocapsid (N) within the

first 3 months after infection. However, Wajnberg et al.[34] and Ogega et al.[35] reported persistent

neutralizing antibodies and memory B cells capable of providing humoral immunity against SARS-CoV-

2 for a longer period of time. Persistent T cells specific to SARS-CoV-2 provide immunity even in

absence of antibodies.[36] However, patients who have antibodies to SARS-CoV-2 are not completely

immune to re-infection during follow up.[9, 37] Boyton and Altmann[38] pointed out that the exact

immunological correlates of protection from SARS-CoV-2 infection are not well understood but the

quality, quantity, and durability of protective immunity elicited by natural infection with SARS-CoV-2

are poor relative to the much higher levels of virus-neutralizing antibodies and T cells induced by the

vaccines[39] European Centre for Disease Prevention and Control[8] also recommended the need for

further studies to elaborate the role of cellular immunity in the prevention of re-infection with SARS-

CoV-2. Phylogenetically distinct variants of SARS-CoV-2 have been implicated in re-infections.[1-5]

Mutations in the SARS-CoV-2 receptor-binding domain (RBD) of the viral spike protein that escape

antibody binding are also implicated in re-infection.[40]

Our study is based on the Cerner Real-World data which lacks the design strengths such as patient

selection and systematic ascertainment methodologies seen in prospective studies. There is heterogeneity

in timing, assays used, and indications for repeat testing. Mandatory serial testing for all patients was not

possible or justified. A total of 9,119 patients with SARS-CoV-2 infection met our inclusion criteria of

serial testing among 110,754 patients with positive SARS-CoV-2 tests. We noted that patients who were

included based on performance of serial testing appeared to have more medical co-morbidities and severe

disease manifestations compared with those who were excluded. Thus, there is perhaps an

underrepresentation of patients with minimal co-morbidities and mild disease manifestations in our analysis. However, such data is more representative of broader population and provides large unselected cohorts. We acknowledge that a positive test after being considered infection free based on serial negative laboratory test may be due to other reasons in addition to re-infection. There may be a relapse or recrudescent of infection with the "first" SARS-CoV-2 inoculum or prolonged shedding of remnant ribonucleic acid (RNA) fragments of the "first" SARS-CoV-2 infection[41] confounded by laboratory errors, or technical limits of RT-PCR assays. The mean time between initial positive RT-PCR testing and subsequent negative change was 6.9 days with a range of 4–15 days and a median of 7 days in a previous study[42] suggesting that it is uncommon to have to have persistent infection beyond 15 days and persistent positive status by RT-PCR for up to 80 days is perhaps the longest period reported in rare cases.[43, 44] Therefore, using a time interval of greater than 90 days should eliminate those with persistence of primary infection. RT-PCR tests have an estimated false negative rate of 13% (95% CI 9 to 19%) for detection of SARS-CoV-2.[45, 46] Therefore, the possibility that some patients classified as re-infection were those with persistent viral shedding and interim RT-PCR test was falsely negative.[47] However, the rate of false negative tests decreases if two false negative tests are used like in ours and other studies.[1-5, 48] We did not have access to any genomic characterization of SARS-CoV-2 detected in re-infected patients and are unable to comment upon the role of phylogenetically distinct variants of SARS-CoV-2 in re-infection. We could not identify the role of any specific therapeutic interventions used during primary infection in preventing re-infection due to lack of data and small number of re-infections.

We were also unable to identify immunodeficiency by laboratory tests or use of immunosuppressive medication which precluded a more detailed analysis.

The exact prevalence of re-infection may be confounded by the selection criteria of our analysis which only included those with serial laboratory tests. This approach eliminates those patients who may have undetected SARS-CoV-2 re-infection because follow up laboratory tests were not performed. We also included those patients who had at least one qualifying ED or inpatient encounter which was considered related to SARS-CoV-2 infection. ED and inpatient encounters are more reliable due to completeness of data recorded in electronic medical records[13] but may exclude some patients with mild disease who were not seen in ED or hospitalized. We acknowledge the effect of variability in hospitalization criteria over time and between institutions on our analysis is not known. We also cannot exclude the possibility that in a certain proportion of patients, some tests may be performed in centers not included in the Cerner Real-World data and thus not available for analysis. The possibility of such occurrence is very low as all included patients had serial tests performed within centers in Cerner Real-World data. The vulnerability for re-infection may be underestimated due to implementation of social distancing policies (March 2020) and universal face mask use (July 2020) recommended by Centers for Disease Control and Prevention.[49, 50] Re-infection may be additionally reduced due to behavioral changes among SARS-CoV-2 infection survivors[51] which may result in high compliance with social distancing measures[52] thus reducing the chance of a re-infection.

Our observations strongly suggest that survivors from SARS-CoV-2 infection must not relax compliance with proven interventions in prevention of SARS-CoV-2 transmission such as social distancing[53] and universal face mask use.[50] Our study supports the position taken by European Centre for Disease Prevention and Control[8] and Centers for Disease Control and Prevention[54] that individuals that have been infected once with SARS-CoV-2 are not always immune and infection prevention/control and contact principles should be followed even after infection. Due to concerns for re-infection, the Centers for Disease Control and Prevention[54] currently recommends vaccination for patients who had SARS-CoV-2 infection after 90 days but acknowledges the limited data is available to support the recommendation.

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CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFEERNCES

1.   First case of covid-19 reinfection detected in the us. Available at:

https://www.ajmc.com/view/first-case-of-covid-19-reinfection-detected-in-the-us. Accessed

February 7.

2.   Tillett RL, Sevinsky JR, Hartley PD, et al. Genomic evidence for reinfection with SARS-CoV-2:

a case study. Lancet Infect Dis **2021**; 21(1): 52-8.

3.   Prado-Vivar B, Becerra-Wong M, Guadalupe JJ, et al. COVID-19 re-infection by a

phylogenetically distinct SARS-CoV-2 variant, first confirmed event in South America.

(September 3, 2020) **2020**.

4.   To KK, Hung IF, Ip JD, et al. COVID-19 re-infection by a phylogenetically distinct SARS-

coronavirus-2 strain confirmed by whole genome sequencing. Clin Infect Dis **2020**.

5.   Van Elslande J, Vermeersch P, Vandervoort K, et al. Symptomatic SARS-CoV-2 reinfection by a

phylogenetically distinct strain. Clin Infect Dis **2020**.

6.   Coronavirus disease (COVID-19). Available at: https://www.who.int/docs/default-

source/coronavirus/situation-reports/20201012-weekly-epi-update-9.pdf. Accessed Febaruary 7.

7.   Reinfection with COVID-19. Available at: https://www.cdc.gov/coronavirus/2019-ncov/your-

health/reinfection.html. Accessed Febaruary 7.

8.   Control ECfDPa. Reinfection with SARS-CoV-2: considerations for public health response.

Available at: https://www.ecdc.europa.eu/sites/default/files/documents/Re-infection-and-viral-

shedding-threat-assessment-brief.pdf. Accessed April 4.

9.   Hall V, Foulkes S, Charlett A, et al. Do antibody positive healthcare workers have lower SARS-

        CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective

        cohort study (the SIREN study), England: June to November 2020. medRxiv **2021**:

        2021.01.13.21249642.

10.   Laird-Maddox M, Mitchell SB, Hoffman M. Integrating research data capture into the electronic

        health record workflow: real-world experience to advance innovation. Perspect Health Inf Manag

        2014; 11(Fall): 1e.

11.   Cerner Corporation. Cerner Provides Access to De-Identified Patient Data for COVID-19

        Research and Vaccine Development. Available at: https://www.cerner.com/newsroom/cerner-

        provides-access-to-de-identified-patient-data-for-covid-19-research-and-vaccine-development.

        Accessed September 16.

12.   Qureshi AI, Baskett WI, Huang W, et al. Facilitating the study of relationships between COVID-

        19 and cardiovascular health outcomes using cerner Real-World COVID-19 deidentified dataset.

        HealthCare Research Journal **2020**; 1(1): 17-28.

13.   Qureshi AI, Baskett WI, Huang W, et al. Acute ischemic stroke and COVID-19: An analysis of

        27 676 patients. Stroke **2021**: STROKEAHA120031786.

14.   Yahav D, Yelin D, Eckerle I, et al. Definitions for coronavirus disease 2019 reinfection, relapse

        and PCR re-positivity. Clin Microbiol Infect **2021**; 27(3): 315-8.

15. Hansen CH, Michlmayr D, Gubbels SM, Molbak K, Ethelberg S. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet **2021**; 397(10280): 1204-12.

16. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med **1998**; 17(8): 857-72.

17. Atti A, Monk E, Hall V, et al. SARS-CoV-2 in the United Kingdom: establishing national surveillance for reinfections and the first two reinfection cases., **(in press)**.

18. Abu-Raddad LJ, Chemaitelly H, Malek JA, et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. Clin Infect Dis **2020**.

19. Lumley SF, O'Donnell D, Stoesser NE, et al. Antibodies to SARS-CoV-2 are associated with protection against reinfection. medRxiv **2020**: 2020.11.18.20234369.

20. Juhn YJ. Risks for infection in patients with asthma (or other atopic conditions): is asthma more than a chronic airway disease? J Allergy Clin Immunol **2014**; 134(2): 247-57; quiz 58-9.

21. Kloepfer KM, Olenec JP, Lee WM, et al. Increased H1N1 infection rate in children with asthma. Am J Respir Crit Care Med **2012**; 185(12): 1275-9.

22. Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med **2004**; 164(20): 2206-16.

23. Hersey P, Prendergast D, Edwards A. Effects of cigarette smoking on the immune system. Follow-up studies in normal subjects after cessation of smoking. Med J Aust **1983**; 2(9): 425-9.

24. Miller LG, Goldstein G, Murphy M, Ginns LC. Reversible alterations in immunoregulatory T cells in smoking. Analysis by monoclonal antibodies and flow cytometry. Chest **1982**; 82(5): 526-9.

25. Tuan J, Spichler-Moffarah A, Ogbuagu O. A new positive SARS-CoV-2 test months after severe COVID-19 illness: reinfection or intermittent viral shedding? BMJ Case Reports **2021**; 14(2): e240531.

26. Sicsic Jr I, Chacon AR, Zaw M, Ascher K, Abreu A, Chediak A. A case of SARS-CoV-2 reinfection in a patient with obstructive sleep apnea managed with telemedicine. BMJ Case Reports **2021**; 14(2): e240496.

27. Larson D, Brodniak SL, Voegtly LJ, et al. A case of early re-infection with SARS-CoV-2. Clin Infect Dis **2020**.

28. Ledford H. Coronavirus reinfections: three questions scientists are asking. Nature **2020**; 585(7824): 168-9.

29. Selvaraj V, Herman K, Dapaah-Afriyie K. Severe, symptomatic reinfection in a patient with COVID-19. R I Med J (2013) **2020**; 103(10): 24-6.

30. Yip MS, Cheung CY, Li PH, Bruzzone R, Peiris JSM, Jaume M. Investigation of antibody-dependent enhancement (ADE) of SARS coronavirus infection and its role in pathogenesis of SARS. BMC Proc **2011**; 5(Suppl 1): P80-P.

31. Ledford H. Why do COVID death rates seem to be falling? Nature **2020**; 587(7833): 190-2.

32. Long QX, Tang XJ, Shi QL, et al. Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. Nat Med **2020**; 26(8): 1200-4.

33. Muecksch F, Wise H, Batchelor B, et al. Longitudinal analysis of serology and neutralizing antibody levels in COVID19 convalescents. J Infect Dis **2020**.

34. Wajnberg A, Amanat F, Firpo A, et al. Robust neutralizing antibodies to SARS-CoV-2 infection persist for months. Science **2020**; 370(6521): 1227-30.

35. Ogega CO, Skinner NE, Blair PW, et al. Durable SARS-CoV-2 B cell immunity after mild or severe disease. J Clin Invest **2021**; 131(7).

36. Sewell HF, Agius RM, Stewart M, Kendrick D. Cellular immune responses to covid-19. BMJ **2020**; 370: m3018.

37. Harvey RA, Rassen JA, Kabelac CA, et al. Real-world data suggest antibody positivity to SARS-CoV-2 is associated with a decreased risk of future infection. medRxiv **2020**.

38. Boyton RJ, Altmann DM. Risk of SARS-CoV-2 reinfection after natural infection. Lancet **2021**; 397(10280): 1161-3.

39. Walsh EE, Frenck RW, Jr., Falsey AR, et al. Safety and immunogenicity of two RNA-based covid-19 vaccine candidates. N Engl J Med **2020**; 383(25): 2439-50.

40. Greaney AJ, Starr TN, Gilchuk P, et al. Complete mapping of mutations to the SARS-CoV-2 spike receptor-binding domain that escape antibody recognition. Cell Host Microbe **2021**; 29(1): 44-57 e9.

41. Henderson DK, Weber DJ, Babcock H, et al. The perplexing problem of persistently PCR-positive personnel. Infect Control Hosp Epidemiol **2020**: 1-2.

42. Ai T, Yang Z, Hou H, et al. Correlation of chest CT and RT-PCR testing for coronavirus disease 2019 (COVID-19) in China: A report of 1014 cases. Radiology **2020**; 296(2): E32-E40.

43. Findings from investigation and analysis of re-positive cases. Available at: https://www.cdc.go.kr/board/board.es?mid=a30402000000&bid=0030. Accessed Febaruary 8.

44. Liu WD, Chang SY, Wang JT, et al. Prolonged virus shedding even after seroconversion in a patient with COVID-19. J Infect **2020**; 81(2): 318-56.

45. Arevalo-Rodriguez I, Buitrago-Garcia D, Simancas-Racines D, et al. False-negative results of initial RT-PCR assays for COVID-19: A systematic review. PLoS One **2020**; 15(12): e0242958.

46. Woloshin S, Patel N, Kesselheim AS. False negative tests for SARS-CoV-2 infection - challenges and implications. N Engl J Med **2020**; 383(6): e38.

47. Agarwal V, Venkatakrishnan AJ, Puranik A, et al. Long-term SARS-CoV-2 RNA shedding and its temporal association to IgG seropositivity. Cell Death Discov **2020**; 6(1): 138.

48. Kanji JN, Zelyas N, MacDonald C, et al. False negative rate of COVID-19 PCR testing: a discordant testing analysis. Virol J **2021**; 18(1): 13.

49. Prevention CfDCa. Social distancing. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/social-distancing.html. Accessed April 4.

50. Brooks JT, Butler JC, Redfield RR. Universal masking to prevent SARS-CoV-2 transmission-the time is now. JAMA **2020**.

51.   Moradi Y, Mollazadeh F, Karimi P, Hosseingholipour K, Baghaei R. Psychological disturbances

of survivors throughout COVID-19 crisis: a qualitative study. BMC Psychiatry **2020**; 20(1): 594.

52.   Wright L, Steptoe A, Fancourt D. Predictors of self-reported adherence to COVID-19 guidelines.

A longitudinal observational study of 51,600 UK adults. The Lancet Regional Health - Europe

2021; 4.

53.   Qureshi AI, Suri MFK, Chu H, Suri HK, Suri AK. Early mandated social distancing is a strong

predictor of reduction in peak daily new COVID-19 cases. Public Health **2021**; 190: 160-7.

54.   Frequently Asked Questions about COVID-19 Vaccination. Available at:

https://www.cdc.gov/coronavirus/2019-

ncov/vaccines/faq.html#:~:text=Yes.,already%20had%20COVID%2D19%20infection. Accessed

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Table 1. Baseline, clinical characteristics, and outcomes of patients with or without re-infection with

SARS-CoV-2

Characteristics	Patients with re-infection No.(%)	Patients without re-infection No.(%)	P-value
Total	63	9056	-
Demographics			
Age (in years)			0.11
< 35	11(17)	1682(18.6)	
35-49	15(24)	1578(17.4)	
50-65	24(38)	2737(30.2)	
> 65	13(21)	3059(33.8)	
Sex			0.66
Men	28(44)	4257(47)	
Women	35(56)	4754(52.5)	
Race/ethnicity			0.03
White, Non-Hispanic	23(37)	3269(36.1)	
African American	10(16)	1599(17.7)	
Asian or Pacific Islander	0(0)	161(1.8)	
Hispanic	16(25)	3110(34.3)	
Others	14(22)	917(10.1)	
Pre-existing medical conditions			
Hypertension	44(70)	5901(65.2)	0.44

Diabetes mellitus	31(49)	3932(43.4)	0.36
Atrial fibrillation	13(21)	1674(18.5)	0.66
Hyperlipidemia	33(52)	4338(47.9)	0.48
Malignancy	6(10)	1256(13.9)	0.32
COPD	22(35)	1659(18.3)	<0.001
Asthma	22(35)	1647(18.2)	<0.001
CKD ESRD	15(24)	2458(27.1)	0.55
Nicotine dependence/Tobacco use	34(54)	2325(25.7)	<.001
Previous cardiac arrest	1(2)	78(0.9)	0.54
Previous stroke	7(11)	777(8.6)	0.48
Previous heart failure	17(27)	1761(19.4)	0.13
Previous STEMI	2(3)	92(1.0)	0.09
Previous NSTEMI	4(6)	408(4.5)	0.48
New events			
Pneumonia	21(33)	4087(45.1)	0.06
Respiratory failure	20(32)	3313(36.6)	0.43
Urinary tract infection	6(10)	1238(13.7)	0.34
Acute kidney injury	17(27)	2299(25.4)	0.78
Septic shock	5(8)	774(8.5)	0.86
Hepatic failure	4(6)	397(4.4)	0.45
Stroke	1(2)	349(3.9)	0.35
Encephalopathy	5(8)	1356(15)	0.12
Thrombosis/pulmonary embolism	3(5)	455(5)	0.92
Cardiac arrest	0(0)	190(2.1)	0.25

STEMI	0(0)	29(0.3)	0.65
NSTEMI	0(0)	223(2.5)	0.21
Heart failure	12(19)	1679(18.5)	0.92
Received intubation/mechanical ventilation	3(5)	762(8.4)	0.46
Outcome[a]			
Non-routine discharge	28(44)	4412(48.7)	0.50
Expired in medical facility	2(3)	504(5.6)	0.41

a: Determined by medical encounter in proximity to fourth laboratory test.

Abbreviations used:

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

COPD: chronic obstructive pulmonary disease

CKD: chronic kidney disease

ESRD: end-stage renal disease

STEMI: ST-elevated myocardial infarction

NSTEMI: non-ST elevated myocardial infarction

Table 2. Medical diagnoses in primary infection and re-infection among patients with re-infection

Diagnoses	Diagnosis rate during first infection No.(%)	Diagnosis rate during second infection No.(%)	P value
Total	63	63	-
Stroke	0(0)	1(2)	0.32
Heart failure	10(16)	3(5)	0.04
Pneumonia	17(27)	7(11)	0.02
Urinary tract infection	3(5)	4(6)	0.70
Acute kidney injury	11(17)	3(5)	0.02
Septic shock	1(2)	1(2)	1
Hepatic failure	3(5)	0(0)	0.08
Respiratory failure	13(21)	6(10)	0.08
Cardiac arrest	0(0)	0(0)	1
Thrombosis/pulmonary embolism	0(0)	2(3)	0.15
Encephalopathy	1(2)	1(2)	1
STEMI	0(0)	0(0)	1
NSTEMI	0(0)	0(0)	1
Received intubation/mechanical ventilation	2(3)	0(0)	0.15

Abbreviations used:

STEMI: ST-elevated myocardial infarction

NSTEMI: non-ST elevated myocardial infarction

Figure 1. Rates of re-infection defined using different cut-off periods for time interval between first and second positive tests

Figure 1